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Enantioselective Reformatsky Reaction of Ketones Catalyzed by Chiral Indolinylmethanol

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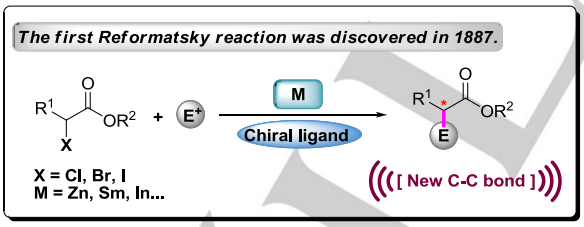
Abstract: A reliable and practical Reformatsky reaction of ethyl iodide acetate with ketones for the synthesis of chiral β-hydroxyl carbonyl compound in good yields and excellent enantioselectivities is presented. Readily available dihydroindole derivative was used as chiral catalyst, ethyl iodide acetate was the nucleophile, and Me_2Zn was the zinc source. The presence of air was found to be essential for the efficient construction of new carbon-carbon bond through a radical pathway.

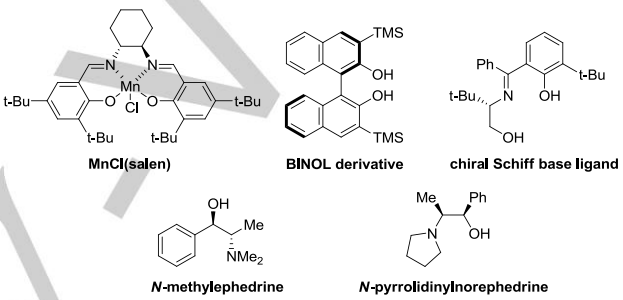
Introduction

Metal-mediated reactions are one of the most effective methods for the construction of carbon-carbon bonds and have been discovered and applied to synthesize a rich variety of complex organic molecules.[1] The classic Reformatsky reaction, which is the zinc-promoted addition of *α*-haloesters to carbonyl compounds to provide *β*-hydroxy esters, has been the most useful methods to form carbon-carbon bonds and an important alternative to the base-induced aldol reaction (Scheme 1).[2] The wide applicability and great versatility of the Reformatsky reaction have made it highly useful organic reactions in synthetic chemistry and laid the foundation for the rapid development of organic chemistry.[3]

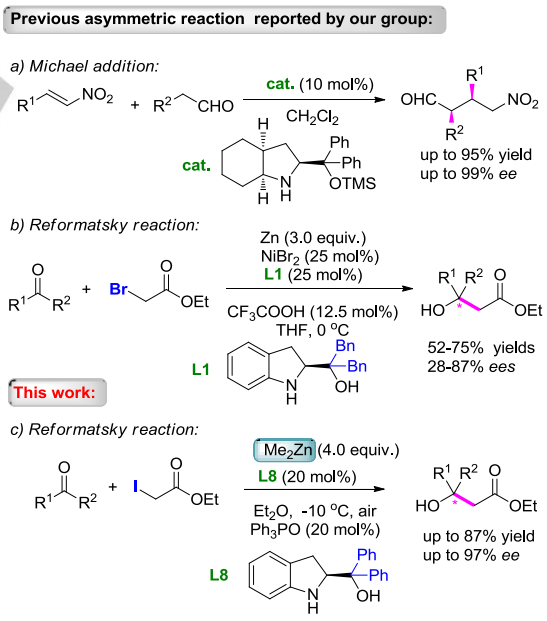


Scheme 1. The classic Reformatsky reaction.

However, the asymmetric Reformatsky reaction remained a great challenge in a long time albeit it has striking applications for the synthesis of many chiral pharmaceuticals. Considerable research efforts have been made using different chiral auxiliaries and ligands, but success has been confined to only a few examples.[4] For instance, a catalytic enantioselective version of this transformation has been successfully reported by using chiral MnCl(salen) complexes,[5] BINOL derivatives,[6] *N*-methylephedrine,[7] *N*-pyrrolidinylnorephedrine,[8] and chiral Schiff base ligands[9] (Scheme 2). Nevertheless, the low yields and enantioselectivities, limited substrate scope have restricted their synthetic utilities. From both fundamental and practical standpoints, it is highly desirable to develop new method for the asymmetric Reformatsky reaction with good stereocontrol.



Scheme 2. Complexes and ligands employed in asymmetric Reformatsky reaction.



Scheme 3. Efficient asymmetric reaction involving chiral indolinylmethanols or derivatives.

As our continuous interests in asymmetric catalysis,[10] we have developed a highly efficient asymmetric Michael reaction using indolinylmethanol catalyst (Scheme 3a).[11] Meanwhile, literatures also documented that chiral indolinylmethanol ligand played an important role in the stereocontrolled diethylzinc addition to aldehydes and ketones.[12-14] Under this background, our group realized the asymmetric zinc powder-promoted

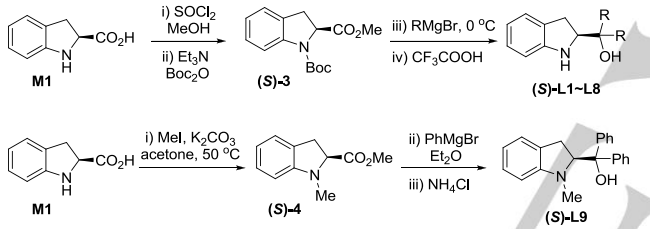
Reformatsky reaction of α-bromoester with ketones using chiral indolinylmethanol ligands (Scheme 3b).[15] Nonetheless, the yields and enantioselectivities are only modarate.

Me_2Zn in the presence of oxygen forms substantial reactive alkyl peroxides (R^1ZnOOR^2),[16] which can initiate radical reactions.[17-18] Hence, we speculated that an effective catalytic enantioselective Reformatsky reaction might be realized via the initiation of Me_2Zn and the proper stereocontrol of chiral Zn-indolinylmethanol complex (Scheme 3c).

Results and Discussion

Synthesis of chiral indolinylmethanols and derivatives

(*S*)-Indoline-2-carboxylic acid **M1** was commercially available, and was chosen as starting material. The reaction of **M1** with thionyl chloride in methanol, followed by protection with Boc_2O provided the corresponding methyl ester (*S*)-**3** in 85% overall yield. Treatment of (*S*)-**3** with RMgBr and the subsequent *N*-Boc deprotection gave the indolinylmethanols (*S*)-**L1~L8** with 34%~50% overall yields (Scheme 5). Reaction of **M1** with iodomethane in the presence of potassium carbonate provided the corresponding methyl ester (*S*)-**4** in 95% yield. Treatment of (*S*)-**4** with PhMgBr under reflux conditions afforded (*S*)-**L9** in 91% yield (Scheme 4).

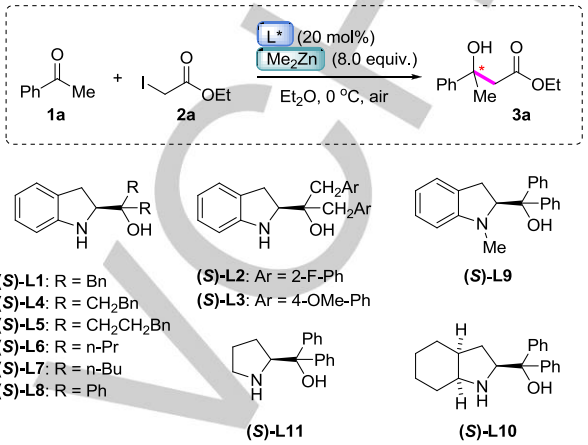


Scheme 4. Preparation of (*S*)-**L1~L9**.

Effect of Ligands

As we were interested to develop new ligands to promote the Reformatsky reaction, at the beginning of this study acetophenone (**1a)** was chosen as the model reaction substrate to study the effects of ligands (Table 1). Different side chains of the chiral indole alcohol derivatives led to different results. With 8.0 equiv. Me_2Zn and Et_2O as the solvent, 71% *ee* and 75% yield were obtained by using (*S*)-**L1** as the ligand (Table 1, entry 1). A slight decrease in enantioselectivity (66% *ee*) and an increase in yield (82%) occured when using (*S*)-**L2** as the ligand (Table 1, entry 2). Almost the same enantioselectivity (70% *ee*) was obtained by using (*S*)-**L3** (Table 1, entry 3). With the longer side chain (*S*)-**L4**, increasing enantioselectivity (81% *ee*) was observed (Table 1, entry 4). However, no increase in enantioselectivity (81% *ee*) was obtained by extending the side chain to (*S*)-**L5** (Table 1, entry 5). Almost the same enantioselectivities were achieved when the side chains R were substituted with *n*-Pr (*S*)-**L6** or *n*-Bu (*S*)-**L7** (Table 1, entries 6 and 7). 85% yields and 90% *ee* were achieved when the side chain was replaced with phenyl group (Table 1, entry 8). Only 60% *ee* was obtained when (*S*)-**L9** was empolyed (Table 1, entry 9), which might be caused by the large steric effect of the substituents. For better contrast, (*S*)-**L10** and (*S*)-**L11** were also tested in this reaction. 81% *ee* was obtained by using (*S*)-**L11**, but only 56% *ee* was obtained by using (*S*)-**L10** as the ligand (Table 1, entries 11 and 10). Longer time was needed and a slight decrease in enantioselectivity (88% *ee*) was obtained when the loading of Me_2Zn was decreased to 4.0 equiv. (Table 1, entry 12).

Table 1. Optimization of ligands in asymmetric Reformatsky reaction.



Entry	Ligand	Time [h]	Yield [%][a]	*ee* [%][b]
1	(*S*)-**L1**	4	75	71
2	(*S*)-**L2**	4	82	66
3	(*S*)-**L3**	4	80	70
4	(*S*)-**L4**	4	76	81
5	(*S*)-**L5**	4	81	81
6	(*S*)-**L6**	4	81	80
7	(*S*)-**L7**	4	92	80
8	(*S*)-**L8**	4	85	90
9	(*S*)-**L9**	4	84	60
10	(*S*)-**L10**	4	91	56
11	(*S*)-**L11**	4	89	81
12[c]	(*S*)-**L8**	12	75	88

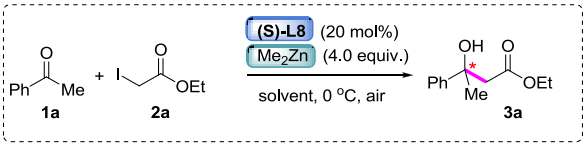
[a] Isolated yield. [b] Determined by OD-H column. [c] 4.0 equiv. Me_2Zn.

Conditions optimization of the Reformatsky reaction with ketones

Several common organic solvents were screened to improve this catalytic system based on the activities (reactivity and enantioselectivity) of (*S*)-**L8**. We used 20 mol% catalyst and 4.0 equiv. Me_2Zn throughout this study. Strong solvent effects were observed as shown in Table 2. Et_2O was the best solvent of this reaction, providing 75% yield and 88% *ee* (Table 2, entry 1). A slight decrease in enantioselectivities (86% *ee* and 85% *ee*) by using toluene and CH_2Cl_2 as the solvents (Table 2, entries 2 and 3). Lower yield (66%) and enantioselectivity (82%) were achieved with the solvent of $CHCl_3$ (Table 2, entry 4). Higher yields but only moderate enantioselectivities were achieved with hexane and THF as the solvents (Table 2, entries 5 and 6). Ligand loading, temperature, and additive were also screened to achieve the best catalytic activity of (*S*)-**L8**. As can be seen in Table 2, a similar yield but only 62% *ee* were obtained when the ligand loading was decreased to 10 mol % (Table 2, entry 7). A slight increase in enantioselectivity (90% *ee*) was observed by using 30 mol% ligand loading (Table 2, entry 8). 90% *ee* was acquired when the reaction proceeded at the temperature of -10 °C (Table 2, entry 9). However, only 81% *ee* was obtained when the reaction temperature was cooled to -20 °C (Table 2, entry

10). The literature has demonstrated that Ph_3PO is a suitable additive for accelerating the Reformatsky reaction, particularly under low temperature.[19] Therefore, 20 mol% of Ph_3PO was added into the reaction, which led to 93.5% *ee* and 83% yield after 5 h (Table 2, entry 11).

Table 2. The influence of solvents on asymmetric Reformatsky reaction.



Entry	Solvent	**L** [mol%]	Time [h]	Yield [%][a]	*ee* [%][b]
1	Et_2O	20	12	75	88
2	toluene	20	12	77	86
3	DCM	20	12	85	85
4	$CHCl_3$	20	12	66	82
5	hexane	20	12	83	64
6	THF	20	12	81	53
7	Et_2O	10	12	80	62
8	Et_2O	30	12	85	90
9	Et_2O[c]	20	12	75	90
10	Et_2O[d]	20	12	73	81
11	Et_2O[e]	20	5	83	93.5

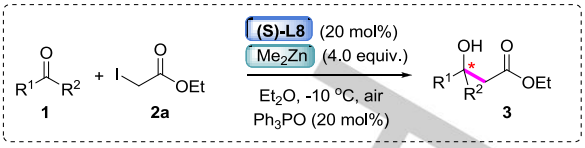
[a] Isolated yield. [b] Determined by OD-H column. [c] The reaction was performed at -10 °C. [d] The reaction was performed at -20 °C. [e] 20% Ph_3PO was added and the reaction was performed at -10 °C.

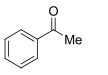
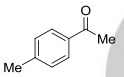
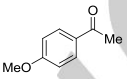
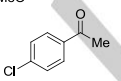
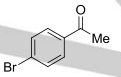
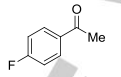
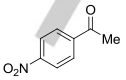
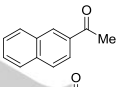
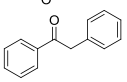
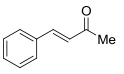
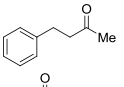
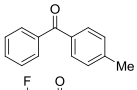
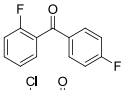
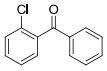
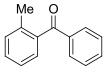
Chiral indolinylmethanol-mediated asymmetric Reformatsky reaction of various ketones

Having established 20 mol% (*S*)-**L8** and Ph_3PO as effective ligand and additive, respectively, and Et_2O as solvent for the enantioselective Reformatsky reaction of ketones, we next investigated the scope of the ketone substrates. A variety of ketones of aromatic, aliphatic and heterocylic were used in the Reformatsky reaction, which provided the desired *β*-hydroxyl ester products in excellent yields and poor to excellent enantioselectivities (Table 3, entries 1-16).

As can be seen in Table 3, the yields obtained in all reactions ranged from good to excellent. Compared with aliphatic and heterocylic ketones (Table 3, entries 11-15), good yields (63%-87%) and enantioselectivities (84%-97% *ee*) were acquired for both electron-rich and electron-poor aryl ketones (Table 3, entries 1-10). In case of 1-indanone and tetralone (Table 3, entries 9 and 10), longer reaction time was needed to ensure good yield. For 1-(4-nitrophenyl)ethanone (Table 3, entry 7), 8.0 equiv. Me_2Zn was needed, and the lowest enantioselectivity (84%) was observed for similar aromatic ketones. Excellent enantioselectivity and moderate yield (91% *ee* and 79% yield) were obtained when acetylthiophene was subjected as substrate (Table 3, entry 11), while good yield but moderate enantioselectivity (64% *ee*) were achieved for furylacetone (Table 3, entry 12). Only moderate enantioselectivity (65% *ee*) was acquired when a larger steric hindrance group at *α*-carbon position was employed (Table 3, entry 13). Good yields but low enantioselectivities (46% *ee* and 20% *ee*) were observed with aliphatic ketones as the substrates (Table 3, entries 14 and 15). Diarylketones were also compatible in this reaction, but low yields were obtained (Table 3, entries 16-19). The location of substituents on the diarylketones determined the

Table 3. Asymmetric Reformatsky reaction of different ketones.



Entry	Substrate	Time [h]	Product **3**	Yield [%][a]	*ee* [%][b]
1		5	**3a**	83	93.5
2		12	**3b**	76	87
3		12	**3c**	73	91
4		8	**3d**	83	86
5		5	**3e**	85	89
6		13	**3f**	82	88
7[c]		13	**3g**	66	84
8		5	**3h**	87	91
9		19	**3i**	63	97
10		19	**3j**	71	89
11		19	**3k**	79	91
12		19	**3l**	82	64
13		13	**3m**	85	65
14		19	**3n**	87	46
15		13	**3o**	85	20
16		19	**3p**	45	5
17		19	**3q**	41	50
18		19	**3r**	43	75
19		19	**3s**	<5	n.d.[d]

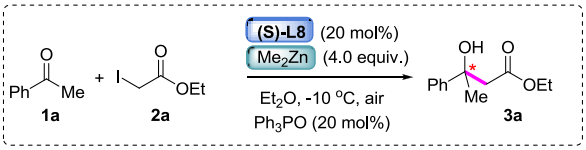
[a] Isolated yield. [b] Determined by Chiral AD-H, AS-H or OD-H column. [c] 8.0 equiv. Me_2Zn was used. [d] n.d. = not determined.

enantioselectivities. For example, a nearly racemic product was acquired by employing the phenyl(*p*-tolyl)methanone as the substrate (Table 3, entry 16). When (2-fluorophenyl)(4-fluorophenyl)methanone was used in the reaction, 50% *ee* was

generated (Table 3, entry 17). The electronegative atom (F or Cl) near the carbonyl was helpful for the nucleophilic addition, the ee increased to 75% when steric Cl atom near the carbonyl (Table 3, entry 18). Nearly no product was obtained when phenyl(*o*-tolyl)methanone was used in the reaction (Table 3, entry 19).

The reaction of acetophenone (**1a**) was also chosen as the model to examine the recyclability of (*S*)-**L8**. After the reaction was completed, the reaction mixture was quenched by 6 *N* HCl and extracted with Et_2O for two times. The recovered aqueous phase was neutralized by 2 *N* NaOH and extracted by Et_2O again. The combined solution was concentrated to acquire the recyclable ligand, which was used again in the reaction. As shown in Table 4, the catalytic activity of (*S*)-**L8** dropped obviously after one cycle. Only 72% *ee* was obtained after the reaction proceeded in 13 h (Table 4, entry 2), which might due to the racemization of ligand under the treatment of acid.

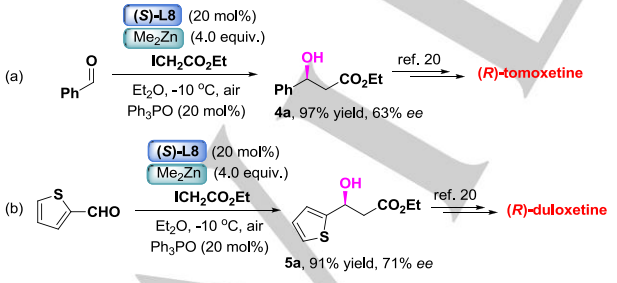
Table 4. Recycling study of (*S*)-**L8.**



Cycle	Time [h]	Yield [%][a]	*ee* [%][b]
1	12	83	91
2	13	75	72

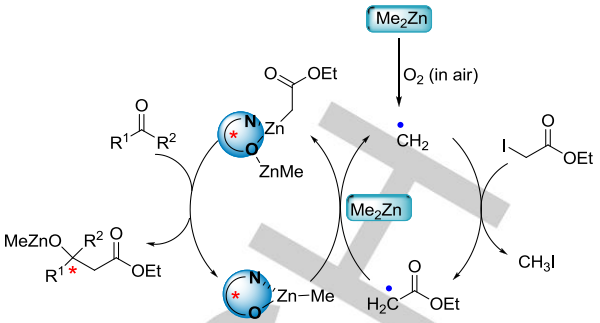
[a] Isolated yield. [b] Determined by OD-H column.

β-hydroxy esters represent a valuable synthons for the synthesis of various functional molecules which are important in bioactive molecules and pharmaceuticals agents, such as anti-depressant medication (*R*)-tomoxetine and (*R*)-duloxetine. Therefore, in order to demonstrate the synthetic utility of this method, the synthesis of chiral drugs was probed. Benzaldehyde and thenaldehyde reacted with ethyl iodide acetate under the standard condition giving **4a** and **5a** in excellent yield and good enantioselectivity (Scheme 5). Even more important, (*R*)-tomoxetine and (*R*)-duloxetine was obtained via ammonolysis, reduction, and condensation.[20]



Scheme 5. Enantioselective syntheses of (*R*)-tomoxetine and (*R*)-duloxetine.

Based on the catalytic cycle proposed by Cozzi for the imino-Reformatsky reaction[21] and the possible mechanism for the Reformatsky reaction with aldehydes and ketones proposed by Feringa,[6a,6b] we supposed a similar radical mechanism for the reaction with ketones as shown in Scheme 6.



Scheme 6. Proposed catalytic cycle for the asymmetric Reformatsky reaction.

Conclusion

New indole alcohols were synthesized in moderate yields and evaluated as chiral ligands in the asymmetric Reformatsky reaction of ketones. (*S*)-Indolin-2-yl-diphenylmethanol (*S*)-**L8** facilitated the reaction of a wide range of ketones, especially for the aromatic ketones, which provided Reformatsky products with good yields and high enantioselectivities (up to 97% *ee*). Further study on the aldehyde substrates and applications in other enantioselective syntheses is still in progress.

Experimental Section

All reactions were performed under air in the dried flask. All solvents were purified by standard drying methods. Unless otherwise stated, commercial reagents were directly used without further purification. Products were purified by flash chromatography using silica gel (200-300 mesh). ^{1}H NMR spectra were determined by Bruker 400 (400 MHz) spectrometer with $CDCl_3$ (δ = 7.26 ppm), or with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{13}C NMR spectra were determined by Bruker (100 MHz) spectrometer with $CDCl_3$ as the internal reference (δ = 77.0 ppm). HPLC analyses were performed with Agilent 1100 instrument using Chiralcel OD-H, Chiralpak AD-H or AS-H columns (0.46 cm diameter × 25 cm length). Optical rotations and MS spectra were recorded on a Perkin Elmer polarimeter (Model 341) and an ESI-ion trap Mass spectrometer (Shimadzu LCMS-IT-TOF) separately.

General procedure for the enantioselective Reformatsky reaction

In a single-neck 25 mL round-bottom flask equipped with a $CaCl_2$ tube, 14.9 mg **(*S*)-L8** (0.05 mmol, 20 mol%) and 13.9 mg (0.05 mmol, 20 mol%) Ph_3PO was added at room temperature. The bottle was taken to -10 °C and Et_2O (5 mL) was added and stirred for about 15 min. 60 μL (0.5 mmol, 2.0 equiv.) ethyl iodide acetate and 0.42 mL Me_2Zn (0.5 mmol, 2 equiv., 1.2 M solution in toluene) was added and immediately a solution of ketone (0.25 mmol) in Et_2O (1 mL) was added at one time. After the addition of ketone, again 0.42 mL Me_2Zn (0.5 mmol, 2 equiv., 1.2 M solution in toluene) was added immediately. The resulting solution was stirred for 5 h and quenched with saturated NH_4Cl (aq.). The organic phase was separated, and the aqueous phase extracted with Et_2O (5 mL×2). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure, then purified by flash chromatography on silica gel (EtOAc/petroleum ether 1:10) to afford the pure product.

(+)-Ethyl 3-hydroxy-3-phenylbutanoate (3a)

$[\alpha]_D^{20}$ = +20.7 (*c* 0.82, CH_2Cl_2). Known compound, colorless liquid, isolated yield 83%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.46-7.43 (m, 2H),

7.35-7.31 (m, 2H), 7.26-7.21 (m, 1H), 4.40 (s, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.98 (d, *J* = 15.9 Hz, 1H), 2.79 (d, *J* = 15.9 Hz, 1H), 1.47 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 171.7, 145.8, 127.2, 125.8, 123.4, 71.7, 59.7, 45.4, 29.7, 13.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 9.49 min, t_{major} = 10.48 min, 93% *ee*.

(+)-Ethyl 3-hydroxy-3-*p*-tolylbutanoate (3b)

$[\alpha]_D^{20}$ = +1.8 (*c* 0.5, CH_2Cl_2). Known compound, colorless liquid, isolated yield 76%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.33 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.33 (s, 1H), 4.06 (qd, *J* = 7.1, 1.2 Hz, 2H), 2.95 (d, *J* = 15.9 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 1.52 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.7, 144.0, 136.4, 128.9, 124.4, 72.6, 60.7, 46.5, 30.7, 20.9, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 9.27 min, t_{major} = 10.70 min, 87% *ee*.

(+)-Ethyl 3-hydroxy-3-(4-methoxyphenyl)butanoate (3c)

$[\alpha]_D^{20}$ = +14.8 (*c* 0.5, CH_2Cl_2). Known compound, colorless liquid, isolated yield 73%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.40-7.32 (m, 2H), 6.89-6.82 (m, 2H), 4.33 (s, 1H), 4.06 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.79 (s, 3H), 2.94 (d, *J* = 15.8 Hz, 1H), 2.76 (d, *J* = 15.8 Hz, 1H), 1.52 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.8, 158.4, 139.1, 125.7, 113.5, 72.5, 60.7, 55.2, 46.5, 30.7, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 18.11 min, t_{major} = 21.65 min, 91% *ee*.

(+)-Ethyl-3-(4-chlorophenyl)-3-hydroxybutanoate (3d)

$[\alpha]_D^{20}$ = +15.1 (*c* 0.42, CH_2Cl_2). Known compound, colorless liquid, isolated yield 83%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.40-7.35 (m, 2H), 7.31-7.27 (m, 2H), 4.43 (s, 1H), 4.06 (qd, *J* = 7.1, 0.9 Hz, 2H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H), 1.51 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.6, 145.5, 132.7, 128.4, 126.0, 72.5, 60.9, 46.2, 30.6, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 9.92 min, t_{major} = 11.42 min, 86% *ee*.

(+)-Ethyl 3-(4-bromophenyl)-3-hydroxybutanoate (3e)

$[\alpha]_D^{20}$ = +13.1 (*c* 0.54, CH_2Cl_2). Known compound, colorless liquid, isolated yield 85%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.51-7.40 (m, 2H), 7.38-7.28 (m, 2H), 4.43 (s, 1H), 4.13-4.01 (m, 2H), 2.93 (d, *J* = 16.0 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H), 1.51 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.5, 146.0, 131.3, 126.4, 120.8, 72.5, 60.9, 46.2, 30.6, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 5.84 min, t_{major} = 6.49 min, 89% *ee*.

(+)-Ethyl 3-(4-fluorophenyl)-3-hydroxybutanoate (3f)

$[\alpha]_D^{20}$ = +13.2 (*c* 0.62, CH_2Cl_2). Known compound, colorless liquid, isolated yield 82%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.45-7.38 (m, 2H), 7.04-6.97 (m, 2H), 4.44 (s, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 2.94 (d, *J* = 15.9 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 1.53 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 171.6, 159.3 (d, *J* = 243 Hz), 141.7 (d, *J* = 3 Hz), 125.3 (d, *J* = 8 Hz), 113.9 (d, *J* = 21 Hz), 71.5, 59.8, 45.5, 29.7, 13.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 0.5 mL/min, UV detection at 208 nm, t_{minor} = 15.75 min, t_{major} = 19.90 min, 88% *ee*.

(+)-Ethyl 3-hydroxy-(4-nitrophenyl)-butanoate (3g)

$[\alpha]_D^{20}$ = +14.3 (*c* 0.41, CH_2Cl_2). Known compound, colorless liquid, isolated yield 66%.[12] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 8.25-8.16 (m, 2H), 7.67-7.61 (m, 2H), 4.59 (s, 1H), 4.08 (qd, *J* = 7.1, 4.1 Hz, 2H), 3.00 (d, *J* = 16.2 Hz, 1H), 2.85 (d, *J* = 16.2 Hz, 1H), 1.56 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.3, 154.3, 125.7, 123.6, 72.7, 61.2, 45.9, 30.5, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 8.09 min, t_{major} = 9.10 min, 84% *ee*.

(+)-Ethyl 3-hydroxy-3-(naphthalen-2-yl)butanoate (3h)

$[\alpha]_D^{20}$ = +17.6 (*c* 0.46, CH_2Cl_2). Known compound, colorless liquid, isolated yield 87%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.93 (s, 1H), 7.84-7.79 (m, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.48-7.41 (m, 2H), 4.54 (s, 1H), 4.07-3.98 (m, 2H), 3.07 (d, *J* = 15.9 Hz, 1H), 2.87 (d, *J* = 15.9 Hz, 1H), 1.62 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.7, 144.3, 133.2, 132.4, 128.2, 128.0, 127.5, 126.1, 125.8, 123.2, 123.1, 72.9, 60.8, 46.4, 30.6, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 8.94 min, t_{major} = 11.42 min, 91% *ee*.

(-)-Ethyl 2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate (3i)

$[\alpha]_D^{20}$ = -17.1 (*c* 0.65, CH_2Cl_2). Known compound, colorless liquid, isolated yield 63%.[6] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.57-7.53 (m, 1H), 7.22-7.13 (m, 2H), 7.06 (d, *J* = 7.0 Hz, 1H), 4.21-4.15 (m, 2H), 4.00 (s, 1H), 2.88-2.71 (m, 4H), 2.12-2.06 (m, 1H), 2.01-1.90 (m, 2H), 1.83-1.72 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.5, 140.7, 136.5, 128.9, 127.4, 126.4, 126.3, 71.1, 60.8, 46.1, 36.4, 29.5, 20.0, 14.2. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 9.65 min, t_{major} = 11.94 min, 97% *ee*.

(+)-(*S*)-Ethyl 2-(1-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate (3j)

$[\alpha]_D^{20}$ = +0.8 (*c* 0.6, CH_2Cl_2). Known compound, colorless liquid, isolated yield 71%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.32 (m, 1H), 7.25-7.19 (m, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 1H), 3.07-3.00 (m, 1H), 2.90-2.78 (m, 2H), 2.69 (d, *J* = 15.8 Hz, 1H), 2.30-2.24 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.7, 146.0, 142.7, 128.5, 126.8, 125.0, 122.9, 81.1, 60.9, 44.0, 40.3, 29.4, 14.2. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 210 nm, t_{minor} = 9.63 min, t_{major} = 12.13 min, 89% *ee*.

(+)-Ethyl-3-hydroxy-3-(thiophen-2-yl)butanoate (3k)

$[\alpha]_D^{20}$ = +14.7 (*c* 0.81, CH_2Cl_2). Known compound, yellowish liquid, isolated yield 79%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.18 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.89 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.74 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.98 (d, *J* = 15.9 Hz, 1H), 2.81 (d, *J* = 15.9 Hz, 1H), 1.63 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.4, 152.3, 126.7, 124.0, 122.0, 71.9, 60.9, 47.0, 31.4, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AS-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 9.00 min, t_{major} = 10.29 min, 91% *ee*.

(+)-Ethyl 3-(furan-2-yl)-3-hydroxybutanoate (3l)

$[\alpha]_D^{20}$ = +6.7 (*c* 0.3, CH_2Cl_2). Known compound, colorless liquid, isolated yield 82%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.32 (d, *J* = 0.8 Hz, 1H), 6.30 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 4.35 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.98 (d, *J* = 15.8 Hz, 1H), 2.72 (d, *J* = 15.8 Hz, 1H), 1.58 (s,

3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.3, 158.5, 141.5, 110.2, 104.6, 69.7, 60.8, 44.5, 27.6, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{major} = 13.18 min, t_{minor} = 19.78 min, 64% *ee*.

(+)-Ethyl-3-hydroxy-3,4-diphenylbutanoate (3m)

$[\alpha]_D^{20}$ = +16.0 (*c* 0.31, CH_2Cl_2). Colorless liquid, isolated yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.07-7.44 (m, 12H), 4.51 (s, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.04-3.17 (m, 3H), 2.81 (d, *J* = 15.9 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.9, 145.6, 136.5, 130.9, 128.1, 127.8, 127.0, 126.6, 125.3, 75.4, 60.7, 50.0, 43.8, 13.9. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{major} = 9.67 min, t_{minor} = 10.88 min, 65% *ee*.

(-)-(*E*)-Ethyl 3-hydroxy-3-methyl-5-phenylpent-4-enoate (3n)

$[\alpha]_D^{20}$ = -8.2 (*c* 0.45, CH_2Cl_2). Known compound, colorless liquid, isolated yield 87%.[6] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.44-7.41 (m, 2H), 7.38-7.33 (m, 2H), 7.31-7.23 (m, 4H), 7.08 (dd, *J* = 6.5, 3.0 Hz, 2H), 4.51 (s, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.10 (dt, *J* = 13.3, 12.2 Hz, 3H), 2.81 (d, *J* = 15.9 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.9, 145.6, 136.5, 131.0, 130.9, 128.1, 128.0, 127.8, 127.0, 126.6, 125.3, 75.4, 60.7, 50.0, 43.8, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 9.12 min, t_{major} = 11.72 min, 44% *ee*.

(-)-Ethyl 3-hydroxy-3-methyl-5-phenylpentanoate (3o)

$[\alpha]_D^{20}$ = -0.4 (*c* 0.58, CH_2Cl_2). Known compound, colorless liquid, isolated yield 85%.[15] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.32-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 1H), 2.77-2.68 (m, 2H), 2.55 (q, *J* = 15.6 Hz, 2H), 1.89-1.81 (m, 2H), 1.33 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 173.0, 142.3, 128.4, 128.3, 125.8, 70.8, 60.7, 45.0, 43.9, 30.3, 26.7, 14.2. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, UV detection at 210 nm, t_{minor} = 16.78 min, t_{major} = 19.12 min, 20% *ee*.

Ethyl-3-hydroxy-3-phenyl-3-(*p*-tolyl)propanoate (3p)

Known compound, colorless liquid, isolated yield 45%.[6] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.42 (d, *J* = 7.6 Hz, 2H), 7.27-7.32 (m, 4H), 7.18-7.24 (m, 1H), 7.10 (d, *J* = 8.1Hz, 2H), 5.04 (s, 1H), 4.06-4.11 (m, 2H), 3.24 (s, 2H), 2.30 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 173.1, 146.3, 143.3, 136.9, 129.1, 128.4, 127.2, 125.8, 125.8, 76.5, 61.1, 45.8, 21.2, 14.2. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 8.85 min, t_{major} = 9.69 min, 5% *ee*.

(+)-Ethyl-3-(2-fluorophenyl)-3-(4-fluorophenyl)-3-hydroxypropanoate (3q)

$[\alpha]_D^{20}$ = +27.7 (*c* 0.79, CH_2Cl_2). Colorless liquid, isolated yield 41%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.79 (td, *J* = 8.1, 1.8 Hz, 1H), 7.44 (dd, *J* = 8.2, 5.4 Hz, 2H), 7.29-7.24 (m, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.02-6.95 (m, 3H), 5.25 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.42 (dt, *J* = 16.3, 8.8 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 173.0, 161.9 (d, *J* = 254 Hz), 159.2 (d, *J* = 254 Hz), 140.7, 132.5 (d, *J* = 12 Hz), 129.5 (d, *J* = 9 Hz), 127.9 (d, *J* = 3 Hz), 127.5 (d, *J* = 2 Hz), 127.2 (d, *J* = 4 Hz), 116.2 (d, *J* = 3 Hz), 114.9 (d, *J* = 21 Hz), 74.5 (d, *J* = 3 Hz), 61.1, 43.9 (d, *J* = 6 Hz), 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 99:1, flow rate 1.0 mL/min, UV detection at 208 nm, t_{minor} = 7.77 min, t_{major} = 8.84 min, 50% *ee*.

(+)-Ethyl-3-(2-chlorophenyl)-3-hydroxy-3-phenylpropanoate (3r)

$[\alpha]_D^{20}$ = +70.7 (*c* 0.29, CH_2Cl_2). Known compound, colorless liquid, isolated yield 43%.[6] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.92 (dd, *J* = 1.3, 7.9 Hz, 1H), 7.20-7.93 (m, 8H), 5.22 (s, 1H), 4.06-4.11 (m, 2H), 3.64 (d, *J* = 15.9 Hz, 1H), 3.48 (d, *J* = 15.9 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 173.1, 143.9, 142.2, 132.2, 131.5, 129.0, 128.3, 128.0, 127.4, 126.6, 126.5, 76.5, 61.1, 42.7, 14.0. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 0.5 mL/min, UV detection at 210 nm, t_{major} = 37.71 min, t_{minor} = 34.42 min, 75% *ee*.

(-)-(*S*)-Ethyl 3-hydroxy-3-phenylpropanoate (4a)

$[\alpha]_D^{20}$ = -25.0 (*c* 1.00, $CHCl_3$). Known compound, colorless liquid, isolated yield 97%.[6] ^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.41-7.28 (m, 5H), 5.19-5.11 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.39 (d, *J* = 3.4 Hz, 1H), 2.77-2.73 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ:* 172.4, 142.6, 128.6, 127.8, 125.7, 70.3, 60.9, 43.4, 14.2. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min, UV detection at 220 nm, t_{major} = 7.09 min, t_{minor} = 9.84 min, 63% *ee*.

(-)-(*S*)-Ethyl 3-hydroxy-3-(thiophen-2-yl)propanoate (5a)

$[\alpha]_D^{20}$ = -17.9 (*c* 1.00, $CHCl_3$). Known compound, colorless liquid, isolated yield 91%.[6] ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.27 (dd, *J* = 4.7, 1.5 Hz, 1H), 6.98 (q, *J* = 3.5 Hz, 2H), 5.42-5.32 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 1H), 2.92-2.81 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 171.9, 146.4, 126.7, 124.9, 123.7, 66.6, 61.0, 43.2, 14.2. The enantiomeric excess was determined by HPLC using Daicel Chiralcel OD-H column, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, UV detection at 220 nm, t_{major} = 11.58 min, t_{minor} = 16.86 min, 71% *ee*.

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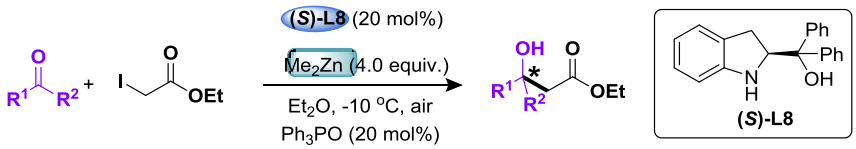
Reformatsky Reaction



Yield up to 87% !!!

Enantioselectivity up to 97% !!!

Asymmetric Reformatsky reaction of ethyl iodide acetate with ketones was realized via the initiation of Me_2Zn and the proper stereocontrol of chiral Zn-indolinylmethanol complex. Various chiral β-hydroxyl carbonyl compounds were obtained in good yields and excellent enantioselectivities (up to 97% ee).